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**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following documents which are listed on Form PTO-1449 (**Exhibit A**) and are also listed below.

Reference items 1-15 are either U.S. Patents or U.S. Patent Application Publications. Pursuant to 37 C.F.R. 1.98(a)(2), copies of references 1-15 are not being submitted.

In addition, copies of the documents listed herein as items 24-28 are not provided because these Hungarian Patents correspond to either WIPO publications or European patents, copies of which are included herein already.

Copies of the documents listed herein as items 16-23 and 29-128 are attached hereto as **Exhibits 1-108**.

1. U.S. Patent No. 5,296,484, issued March 22, 1994, Coghlan, M. J. et al.;
2. U.S. Patent No. 5,646,130, issued July 8, 1997, Shi, G. H.;
3. U.S. Patent No. 5,877,180, issued March 2, 1999, Linden et al.;
4. U.S. Patent No. 5,889,026, issued March 30, 1999, Alanine et al.;

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5. U.S. Patent No. 5,935,964, issued August 10, 1999, Baraldi et al.;
6. U.S. Patent No. 6,117,878, issued September 12, 2000 to Linden, J.;
7. U.S. Patent No. 6,465,456, issued October 15, 2002, Springer et al.;
8. U.S. Patent No. 6,916,804, issued July 12, 2005 to Castelhana, A. et al.;
9. U.S. Patent No. 7,202,252, issued April 10, 2007, Wilson et al.;
10. U.S. Patent Application Publication No. 2003-0139427 A1, published November 1, 2005 (Castelhana, A. et al.);
11. U.S. Patent Application Publication No. 2003-0029067-A1, published 12/11/2003 (Castelhana, A. et al.);
12. U.S. Patent Application Publication No. 2005-0119271 A1, published June 2, 2005 (Castelhana, A. et al.);
13. U.S. Patent Application Publication No. 2004-0082599-A1, published 4/29/2004 (Castelhana, A. et al.);
14. U.S. Patent Application Publication No. 2005-0043332 A1, published 2/24/2005 (Castelhana, A. et al.);
15. U.S. Patent Application Publication No. 2008-0070936,

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published March 20, 2008 (Castelhana, A. et al.);

16. PCT International Application No. WO 97/47601, published December 18, 1997 **(Exhibit 1)**;
17. PCT International Application No. WO 99/64407, published December 16, 1999 **(Exhibit 2)**;
18. PCT International Application No. WO 99/08460, published February 18, 1999 **(Exhibit 3)**;
19. PCT International Application No. WO 00/03741, published January 27, 2000 **(Exhibit 4)**;
20. PCT International Application No. WO 2003/053361, published July 3, 2003 **(Exhibit 5)**;
21. PCT International Application No. WO 2003/053366, published July 3, 2003 **(Exhibit 6)**;
22. European Patent Application No. EP 0 729 758 A2, published September 4, 1996 **(Exhibit 7)**;
23. European Patent No. EP 1246623 B1, published August 9, 2006 **(Exhibit 8)**;
24. Hungarian Patent No. HU P9303515 (corresponds to WO 94/13676);
25. Hungarian Patent No. HU P9501230 (corresponds to EP 0682027);

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26. Hungarian Patent No. HU P9602016 (corresponds to WO 95/19970);
27. Hungarian Patent No. HU P9402829 (corresponds to WO 93/20078);
28. Hungarian Patent No. HU P9602017 (corresponds to WO 95/19774);
29. Abbracchio M., et al., (1997) "Modulation of Apoptosis by Nervous System: a Possible Role for the A<sub>3</sub> Receptor", Ann. NY. Acad. Sci., 825: 11-22 (**Exhibit 9**);
30. Aoyama S. et al. (2000) "Rescue of Locomotor Impairment in Dopamine D2 Receptor-Deficient Mice by an Adenosine A2a Receptor Antagonist" J. Neuroscience 20(15):5848-5852 (**Exhibit 10**);
31. Avila, M.Y. (2001) "A1-A2a and A3-Subtype Adenosine receptors Modulate Intraocular Pressure in the Mouse" J. of Pharmacol. 241-245 (**Exhibit 11**);
32. Baraldi, P.G. et al. (1996) "Pyrazolo [4,3-e]-1,2,4 triazolo [1,5-c]pyrimidine Derivatives: Potent and Selective A2a Adenosine Antagonists" J. Med. Chem. 39:1164-1171 (**Exhibit 12**);
33. Baraldi P., et al., (2000) "New potent and selective human adenosine A<sub>3</sub> receptor antagonists", Tips, 21: 456-459 (**Exhibit 13**);

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34. Baraldi et al. "Pyrazolo-triazolo-pyrimidine derivatives as adenosine receptor antagonists: a possible template for adenosine receptor subtypes", *Curr. Pharm. Design* 8: 2299-2332, 2002 **(Exhibit 14)**;
35. Baraldi, P.G. et al., (1999) "A1 and A3 adenosine receptor agonists: an overview." *Expert Opinion on Therapeutic Patents*, 9(5):515-527 **(Exhibit 15)**;
36. Baraldi, P.G. et al., (2004) "Allosteric modulators for the A1 adenosine receptor." *Expert Opinion on Therapeutic Patents*, 14(1):71-79 **(Exhibit 16)**;
37. Baraldi P.G. (2003) "Recent developments in the field of A2A and A3 adenosine receptor antagonists" *Eur. J. Med. Chem.* 38(4) 367 **(Exhibit 17, abstract only)**;
38. Blazynski C., (1990) "Discrete Distributions of Adenosine Receptors in Mammalian Retina", Journal of Neurochemistry, 53: 648-655 **(Exhibit 18)**;
39. Borman, S. (2001) "A3 Receptors" *C&EN*, 79(7), 37 **(Exhibit 19)**;
40. Braas K.M., et al., (1987) "Endogenous adenosine and adenosine receptors localized to ganglion cells of the retina", Proceedings of the National Academy of Science, 84: 3906-3910 **(Exhibit 20)**;
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42. Bremer et al. (2002) "Therapy of Crohn's Disease in Childhood", Expert Opin. Pharmacother. 3(7): 809-825 **(Exhibit 22)**;
43. Broach, J. R., et al., (1983) "Vectors for high level, inducible expression of cloned genes in yeast", Inouye (ed)., Experimental Manipulation of Gene Expression. Academic Press, New York, 83-117 **(Exhibit 23)**;
44. Casavola V., et al., (1998) "Adenosine A3 receptor activation increases cytosolic calcium concentration via calcium influx in A6 cells", Drug Development Research, 43 (1): 62 **(Exhibit 24)**;
45. Cheng, Y. and Prusoff, W. H. (1973) "Relationship Between The Inhibition Constant ( $K_i$ ) And The Concentration Of Inhibitor Which Causes 50 Per Cent Inhibition ( $I_{50}$ ) Of An Enzymatic Reaction", Biochem. Pharmacol., 22: 3099-3109 **(Exhibit 25)**;
46. Christianson, T. W. et al., (1992) "Multifunctional yeast high-copy-number shuttle vectors", Gene, 110: 119-122 **(Exhibit 26)**;
47. Christofi, F.L. et al. (2001), "Differential Gene Expression of Adenosine A1, A2a, A2b, and A3 Receptors in the Human Enteric Nervous System", J. Comp. Neurol.

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439(1): 46-64 **(Exhibit 27);**

48. Coney, A.M. et al. (1998) "Role of Adenosine and its Receptors in the Vasodilation Induced in the Cerebral Cortex of the Rat by Systemic Hypoxia" J. Physiol. 509:507-518 **(Exhibit 28);**
49. Cooper, J.A. (1995) "Adenosine Receptor-induced Cyclic AMP Generation and Inhibition of 5-hydroxytryptamine release in Human Platelets" Br. J. Clin. Pharmacol. 40:43-50 **(Exhibit 29);**
50. Corset, V. et al. (2000), "Netrin-1-mediated axon outgrowth and cAMP production requires interaction with adenosine A2b receptor", Nature, 407 (6805): 747-750 **(Exhibit 30);**
51. Dubey, R.K. et al. (2001), "A<sub>2B</sub> Receptors Mediate the Antimitogenic Effects of Adenosine in Cardiac Fibroblasts", Hypertension 37: 716-721 **(Exhibit 31);**
52. Duzic, E. et al., (1992) "Factors Determining the Specificity of Signal Transduction by Guanine Nucleotide-binding Protein-coupled Receptors", J. Biol. Chem., 267: 9844-9851 **(Exhibit 32);**
53. Ezeamuzie C., et al., (1999), British Journal of Pharmacology, 127: 188-194 **(Exhibit 33);**
54. Faivre, K. et al., (2001) "Suppression of Cellular Invasion by Activated G-Protein Subunits G $\alpha$ o, G $\alpha$ i1, and

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55. Feoktistov, I. and Biaggioni, I., (1997) "Adenosine A<sub>2B</sub> Receptors", Pharmacol. Rev. 49(4): 381-402 **(Exhibit 35)**;
56. Feoktistov, I. et al., (2002) "Differential Expression of Adenosine Receptors in Human Endothelial Cells", Circulation Research 90: 531-538 **(Exhibit 36)**;
57. Fishman P (2003) "Pharmacology and therapeutic applications of A3 receptor subtype" Curr. Top. Med. Chem. 3(4): 463-9 **(Exhibit 37)**;
58. Fozard J., et al., (1996) "Mast cell degranulation following adenosine A3 receptor activation in rats", European Journal of Pharmacology, 298: 293-297 **(Exhibit 38)**;
59. Franco M., et al., (1999) "Adenosine Regulates Renal Nitric Oxide Production in Hypothyroid Rats", Journal of the American Society of Nephrology, 1681-1688 **(Exhibit 39)**;
60. Gao, Z. et al., "A<sub>2B</sub> Adenosine and P2Y<sub>2</sub> Receptors Stimulate Mitogen-activated Protein Kinase in Human Embryonic Kidney-293 Cells" *J. Bio. Chem.* (1999) 274(9): 5972-5980 **(Exhibit 40)**;
61. Ghiardi, G.J. et al. (1999) "The Purine Nucleoside Adenosine in Retinal Ischemia-Reperfusion Injury" Vision



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62. GenBank accession # S46950 (**Exhibit 42**);
63. GenBank accession numbers S45235 and S56143 (**Exhibit 43**);
64. Grant, M.B. et al., (2001) "Proliferation, Migration, and ERK Activation in Human Retinal Endothelial Cells through A<sub>2B</sub> Adenosine Receptor Stimulation", Invest. Ophthalmol. Vis. Sci. 42(9): 2068-2073 (**Exhibit 44**);
65. Guerra L., et al., (1998) "Adenosine A<sub>3</sub> receptor activation increases cytosolic calcium influx in A6 cells", Nephrology Dialysis Transplantation, 13 (6): A5 (**Exhibit 45**);
66. Guo, Y. et al., (2001) "Targeted deletion of A<sub>3</sub> adenosine receptor confers resistance to myocardial ischemic injury and does not prevent early preconditioning." *J Mol Cell Cardiol*, 33:825-830 (**Exhibit 46**);
67. Haynes, J. Jr. et al., (1999) "5-(N-ethylcarboxamido) adenosine desensitizes the A<sub>2b</sub>-adenosine receptor in lung circulation", Am. J. Physiol. 276(6): H1877-H1883 (**Exhibit 47**);
68. Herndon, J.L. et al., (1992) Herndon, J.L. et al., "Ketanserin Analogs: Structure-Affinity Relationships for 5-HT<sub>2</sub> and 5-HT<sub>1C</sub> Serotonin Receptor Binding", J. Med. Chem. 35(26): 4903-4910 (**Exhibit 48**);

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69. Hoeschst India Ltd., India "Pharmacologically active pyrimido "[4,5-b]indoles and their salts." Database accession No. 106:84629 HCA XP002121648 **(Exhibit 49)**;
70. Kanda, T. et al. (1998) "Adenosine A2a Receptors Modify Motor Function in MPTP-treated Common Marmosets" Neuroreport 9:2857-2860 **(Exhibit 50)**;
71. Kanda, T. et al. (2000) "Combined Use of the Adenosine A2a Antagonist KW-6002 with L-DOPA or with Selective D1 or D2 Dopamine Agonists Increases Antiparkinsonian Activity but not Dyskinesia in MPTP-Treated Monkeys" Experimental Neurology 162:321-327 **(Exhibit 51)**;
72. Kang, Y. et al., (1990) "Effects of Expression of Mammalian G $\alpha$  and Hybrid Mammalian-Yeast G $\alpha$  Proteins on the Yeast Pheromone Response Signal Transduction Pathway", Mol. Cell. Biol., 10: 2582-2590 **(Exhibit 52)**;
73. Kiichiro, K. et al. "Synthesis of pyrazinecarboxylic acid derivs. - (II) derivs. of 3-aminopyrazinecarboxylic acid" Chem. Abstracts 56:8713, Chemical Abstracts Service, Columbus Ohio, US XP 002121649 **(Exhibit 53)**;
74. Kiritsy, J.A. et al., (1978) "Synthesis and Quantitative Structure-Activity Relationships of Some Antibacterial 3-Formylrifamycin SV N-(4-Substituted phenyl) piperazinoacethydrazones" J. Med. Chem. 21(12): 1301-1307 **(Exhibit 54)**;
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76. Knutsen, L.J.S. et al. (2001) Curr. Opin. Invest. Drugs  
2(5):668-673 (**Exhibit 56**);
77. Kopf, S.R. et al. (1999) "Adenosine and Memory Storage:  
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Psychopharmacology 146:214-219 (**Exhibit 57**);
78. Li, J.M. et al. (1998) "Adenosine A2a Receptors Increase  
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80:357-364 (**Exhibit 58**);
79. Linden, J. et al., (1998) "The Structure and Function of  
A1 and A2B Adenosine Receptors" Life Sciences 62(17-18):  
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80. Meade et al., PubMed Abstract (Life Sci. 69(11):1225-40)  
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81. Mitchell, C.H. et al., "Adenosine A3 Receptor Activation  
Reduces Cell Volume and Activates Cl<sup>-</sup> Current in Human  
Ciliary Epithelial Cells", *FASEB J*, A134 (Abstract only)  
(**Exhibit 61**);
82. Michell, C.H. (1999) "A3 adenosine receptors regulate Cl-  
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83. Mirabet, M. et al., (1999) "Expression of A2B adenosine receptors in human lymphocytes: their role in T cell activation" J. Cell. Sci. 112(4): 491-502 **(Exhibit 63);**
84. Montesinos, M.C. et al. (2002) "Adenosine Promotes Wounds Healings and Mediates Angiogenesis in Response to Tissue Injury Via Occupancy of A2a Receptors" American Journal of Pathology 160(6):2009-2018 **(Exhibit 64);**
85. Müller, C.E. et al., (2002) J. Med. Chem. 45(16): 3440-3450 **(Exhibit 65);**
86. Müller, C.E. (2001) "A<sub>3</sub> Adenosine Receptor Antagonists" Mini Reviews in Med. Chem. 1(4): 339 **(Exhibit 66);**
87. Nagarathnam, D. et al., (1998) "Design and Synthesis of Novel  $\alpha$ 1a Adrenoceptor-Selective Dihydropyridine Antagonists for the Treatment of Benign Prostatic Hyperplasia", J. Med. Chem. 41(26): 5320-5333 **(Exhibit 67);**
88. Nishiyama, A. et al. (2001) "Interactions of Adenosine A1 and A2 a Receptors on Renal Microvascular Reactivity" Am. J. Physiol. Renal Physiol. 280:F406-F414 **(Exhibit 68);**
89. Ohana G., et al., (2001) "Differential Effect of Adenosine on Tumor and Normal Cell Growth: Focus on the A3 Adenosine Receptor", Journal of Cellular Physiology, 186: 19-23 **(Exhibit 69);**

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90. Phillis, J.W. (1995) "The Effects of Selective A1 and A2a Adenosine Receptor Antagonists on Cerebral Ischemic Injury in the Gerbil **(Exhibit 70);**
91. Polosa (2002) "Adenosine-receptor subtypes: their relevance to adenosine-mediated responses in asthma and chronic obstructive pulmonary disease", Eur. Respir. Journal 20,488-496 **(Exhibit 71);**
92. Priego, E.-M. et al., (2002) J. Med. Chem., 45(16): 3337-3344 **(Exhibit 72);**
93. Ralevic, V. And Burnstock, G., (1998) "Receptors for Purines and Pyrimidines", Pharmacol. Rev. 50(3): 413-492 **(Exhibit 73);**
94. Regnauld, K. et al., (2002) "G-protein  $\alpha$ olf subunit promotes cellular invasion, survival, and neuroendocrine differentiation in digestive and urogenital epithelial cells", Oncogene 21(25): 4020-4031 **(Exhibit 74);**
95. Regulation of Downstream Effectors By GPCRs, (1999) FASEB J., Abstracts 147.1-147.6 **(Exhibit 75);**
96. Reshkin J., et al., (2000) "Activation of A3 Adenosine Receptor Induces Calcium Entry and Chloride Secretion in A6 Cells", J. Membrane Biol., 178: 103-113 **(Exhibit 76);**
97. Robinson, "Medical Therapy of Inflammatory Bowel Disease for the 21st Century", Eur J Surg. Suppl 582:90-98, 1998 **(Exhibit 77);**

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98. Sawynok J., et al., (1997) "Adenosine A3 receptor activation produces nociceptive behaviour and edema by release of histamine and 5-hydroxytryptamine", European Journal of Pharmacology, 333: 1-7 **(Exhibit 78)**;
99. Shiozaki, S. et al. (1999) "Actions of Adenosine A2a Receptor Antagonist KW-6002 on Drug-induced Catalepsy and hypokinesia Caused by Reserpine of MPTP" Psychopharmacology 147:90-95 **(Exhibit 79)**;
100. Simone, Oncology: Introduction Cecil Textbook of Medicine, 20th Edition, Vol. 1, pp. 1004-1010, 1996 **(Exhibit 80)**;
101. Singh et al., "Immune therapy in inflammatory bowel disease and models of colitis", British Journal of Surgery, 88: 1558-1569, 2001 **(Exhibit 81)**;
102. Strohmeier, G. R. et al., (1995) "The A<sub>2b</sub> Adenosine Receptor Mediates cAMP Responses to Adenosine Receptor Agonists in Human Intestinal Epithelia", J. Bio. Chem., 270: 2387-2394 **(Exhibit 82)**;
103. Svenningsson, P. et al. (1999) "Distribution, Biochemistry and Function of Striatal Adenosine A2a Receptors" Prog. Neurobiol. 59(4):355-396 **(Exhibit 83)**;
104. Tanaka, H. et al.' "Preparation and formulation of fused pyrimidine compounds as CRF receptor antagonists." Database accession no. 129:109098 HCA XP002121647

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**(Exhibit 84);**

105. Taomoto, M. et al. (2000) "Localization of Adenosine A2 Receptor in Retinal Development and Oxygen-Induced Retinopathy" Investigative Ophthalmology & Visual Science 41(1):230-243 **(Exhibit 85);**

106. Van Niel, M.B. et al., "Fluorination of 3-(3-(Piperidin-1-yl)propyl)indoles and 3-(3-(Piperazin-1-yl)propyl)indoles Gives Selective Human 5-HT<sub>1D</sub> Receptor Ligands with Improved Pharmacokinetic Profiles" J. Med. Chem. (1999) 42(12): 2087-2104 **(Exhibit 86);**

107. Varani, K. et al. (1998) "[<sup>3</sup>H]-SCH 58261 Labelling of Functional A<sub>2a</sub> Adenosine Receptors in Human Neutrophil Membranes" Br. J. Pharmacol. 123:1723-1731 **(Exhibit 87);**

108. Von Lubitz D., et al., (1999) "Stimulation of Adenosine A<sub>3</sub> Receptors in Cerebral Ischemia", Ann. NY. Acad. Sci., 890: 93-106 **(Exhibit 88);**

109. Von Lubitz, D., et al., (1999) "Chronic administration of adenosine A<sub>3</sub> receptor agonist and cerebral ischemia: neuronal and glial effects", European Journal of Pharmacology, 367: 157-163 **(Exhibit 89);**

110. West, R.A. et al. (1961) "2-alkyl(aryl)-and 2,7-dimethyl-4-substituted aminopyrrolo[2,3-d]pyrimidines." J. Org. Chem., 26:3809-3812 **(Exhibit 90);**

111. Yan, Luo et al. (2003) Expert Opinion on Emerging Drugs,

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vol. 8, no. 2 pp. 537-576 **(Exhibit 91);**

112. Yao Y., et al., (1997) "Adenosine A3 Receptor Agonists Protect HL-60 and U-937 Cells from Apoptosis Induced by A3 Antagonists", Biochemical And Biophysical Research Communications, 232: 317-322 **(Exhibit 92);**

113. Zhao Z., et al., (2000) "A role for the A3 Adenosine receptor in determining tissue levels of cAMP and blood pressure: studies in knock-out mice", Biochimica et Biophysica Acta, 1500: 280-290 **(Exhibit 93);**

114. International Search Report issued in PCT International Application No. PCT/US99/12135, filed June 1, 1999 **(Exhibit 94);**

115. International Search Report issued in PCT International Application No. PCT/US00/32702, filed December 1, 2000 **(Exhibit 95);**

116. International Search Report issued in PCT International Application No. PCT/US2001/045280, filed November 30, 2001 **(Exhibit 96);**

117. International Search Report issued in PCT International Application No. PCT/US2002/38055, filed November 27, 2002 **(Exhibit 97);**

118. International Search Report issued in PCT International Application No. PCT/US2002/40890, filed December 20, 2002 **(Exhibit 98);**



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119. International Search Report issued in PCT International Application No. PCT/US2002/41273, filed December 20, 2002 **(Exhibit 99)**;
120. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US99/12135 **(Exhibit 100)**;
121. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US00/32702 **(Exhibit 101)**;
122. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2001/045280, filed November 30, 2001 **(Exhibit 102)**;
123. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2002/38055, filed November 27, 2002 **(Exhibit 103)**;
124. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2002/40890, filed December 20, 2002 **(Exhibit 104)**;
125. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2002/41273, filed December 20, 2002 **(Exhibit 105)**;
126. Supplemental European Search Report; for EP Application No. 02 80 5676; issued 2/7/2005 **(Exhibit 106)**;

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127. Partial European Search Report for EP Application No. 06  
01 6543.8; completed 10/4/2006 (**Exhibit 107**); and

128. Partial European Search Report; for EP Application No. 01  
99 7029; completed 12/21/2004 (**Exhibit 108**).

Applicants request that the Examiner review the references and  
make them of record in the subject application.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed \$120.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

*Gary J. Gershik* 5/9/08  
John P. White  
Reg. No. 28,678  
Gary J. Gershik  
Reg. No. 39,992

Date

*Gary J. Gershik*  
John P. White  
Registration No. 28,678  
Gary J. Gershik  
Registration No. 39,992  
Attorneys for Applicants  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, New York 10036  
(212) 278-0400

**EXHIBIT A**

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